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Prevention of Nausea and Vomiting Associated with Stem Cell Transplant: Results of a Prospective, Randomized Trial of Aprepitant Used with Highly Emetogenic Preparative Regimens

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A B S T R A C T

Uncontrolled delayed nausea and vomiting remains a problem after high-dose preparative regimens used for autologous and allogeneic hematopoietic stem cell transplants. Recently, aprepitant was approved for highly and moderately emetogenic chemotherapy, and, in particular, is effective for decreasing delayed emesis. To evaluate its safety and efficacy in the transplantation setting, we performed a randomized, placebo-controlled, phase 3 trial of aprepitant in combination with ondansetron and dexamethasone in patients treated with ablative preparative regimens. Patients were randomized to receive oral aprepitant or placebo daily with oral ondansetron and dexamethasone during and for 3 days after the completion of the preparative regimen in this prospective randomized, double-blind study. The primary objective was complete response (CR) rate, defined as no emesis with no or mild nausea. Other endpoints included number of emetic episodes, nausea severity assessed using a 100-mm visual analog scale (VAS), the need for rescue antiemetics, and transplantation outcome, including regimen-related toxicity. One hundred eighty-one patients were randomized and 179 patients were eligible for analysis. Overall, CR rates were 81.9% for the aprepitant and 65.8% for the placebo arms ($P < .001$). Percentages of patients with no emesis all days were 73.3% for aprepitant and 22.5% placebo ($P < .001$). Mean VAS scores were 16.6 mm aprepitant and 16.9 mm placebo (NS), and there were no differences in the amount of rescue antiemetics used, regimen related toxicity, engraftment, or transplantation outcome. Aprepitant in combination with dexamethasone and ondansetron significantly decreased emesis and significant nausea, whereas not increasing RRT or affecting short-term survival but had no significant impact on the use of PRN antiemetics, or overall VAS nausea scores.

INTRODUCTION

Prevention of nausea and vomiting remains a challenge for patients receiving highly emetogenic preparative regimens before stem cell transplant despite the use of 5-HT_3 antagonists [1]. The 5-HT_3 antagonists are effective in preventing acute nausea and vomiting in this patient group; however, control decreases rapidly over the days of the preparative regimen from 90% on day 1 to 10% by the end of the preparative regimen [2]. This is likely because serotonin release is not a major etiologic factor in the delayed phase of chemotherapy-induced nausea [3].

Aprepitant is a neurokinin-1 antagonist that interferes with the effects of the neuropeptide, substance P [4]. In animal studies, neurokinin-1 antagonists are effective in controlling emesis induced by emetogenic stimuli against which 5-HT_3 antagonists have little effect, including apomorphine, loperamide, copper sulfate, and motion-induced emesis [4,5]. It is Food & Drug Administration (FDA)-approved and administered for 3 days to patients receiving highly and moderately emetogenic chemotherapy, where its major impact is in preventing delayed nausea and vomiting in naively treated patients [6-10]. The etiology of nausea and vomiting in the stem cell transplant population is multifactorial and includes anticipatory effects in these typically heavily treated patients, side effects of prophylactic antibiotics and narcotic analgesics, and the high-dose preparative regimens that lead to a poor end-of-regimen control rate, making aprepitant an attractive addition to standard antiemetic regimens for these patients.

However, as transplantation preparative regimens typically take up to a week to administer, it is important to provide effective drug levels throughout the preparative regimen and 3 days beyond or significantly longer than the drug is currently used, which could have toxicity implications. When used only 3 days as approved by the FDA, aprepitant is a substrate for and moderate inhibitor of CYP3A4 and a mild inducer of CYP2C9. However, when used for more than 7 days, aprepitant may actually act as an inducer of CYP3A4 [11,12]. As both etoposide and high-dose cyclophosphamide are metabolized by CYP3A4, so aprepitant could theoretically affect the transplantation outcome as well as regimen-related toxicity (RRT) in this setting.

Therefore, we conducted a prospective, randomized, double-blind phase III trial of aprepitant for the prevention of

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nausea and vomiting associated with highly emetogenic preparative regimens before stem cell transplant (SCT), in which the aprepitant was given daily during and for 3 days after the preparative regimen finished with endpoints of both efficacy and toxicity as measured by engraftment, RRT, and progression-free survival (PFS) and overall survival (OS) [13]. As such, the trial required an investigational new drug number due to its non-FDA-approved dosing and was registered at ClinicalTrials.gov Identifier NCT00781768.

PATIENTS AND METHODS

Design

This study was a single-center, comparative, randomized, double-blind, phase III trial designed to evaluate the efficacy of oral aprepitant (Emend; Merck & Co., West Point, PA) in combination with ondansetron and dexamethasone in the prevention of acute and delayed nausea and vomiting compared to ondansetron and dexamethasone alone in patients receiving highly emetogenic preparative regimens before autologous or allogeneic SCT. The protocol was approved by the institutional review board, and written informed consent was obtained from each patient.

Patients

Eligible patients were at least 18 years of age, had malignant disease, consumed <5 alcoholic drinks per day in the past 1 year, and were scheduled to receive 1 of 5 myeloablative high-dose cyclophosphamide preparative regimens before SCT: total body irradiation (TBI)/etoposide/cyclophosphamide (Cy) [14] (TBI 1200 Gy fractionated into 8 doses on days -8, -7, -6, and -5, etoposide 60 mg/kg i.v. over 4 hours on day -4, Cy 100 mg/kg i.v. over 2 hours on day -2), busulfan (Bu)/Cy [15,16] (oral Bu 0.875 mg/kg/dose or i.v. Bu 0.8 mg/kg/dose every 6 hours × 16 doses given on days -7, -6, -5, -4 and Cy 60 mg/kg i.v. over 1 hour on days -3 and -2), etoposide, cytarabine, melphalan/VP/Cy [17] (carmustine 15 mg/kg i.v. over 2 hours on day -6, etoposide 60 mg/kg i.v. over 4 hours on day -4, Cy 100 mg/kg i.v. over 2 hours on day -2), and TBI/Cy [18] (TBI = 1200 cGy fractionated into 8 doses on days -7, -6, -5, and -4, and Cy 60 mg/kg i.v. over 1 hour on days -3 and -2). Patients were required to have an estimated creatinine clearance of at least 50 mL/minute and normal liver function, defined as a total bilirubin less than 1.5 × upper limit of normal and an aspartate aminotransferase <2 × upper limit of normal.

Procedures

Patients who met the eligibility criteria were stratified by gender [13] and randomized to 1 of 2 treatments: dexamethasone 7.5 mg i.v. once daily and ondansetron 8 mg orally every 8 hours on each day of the preparative regimen plus 1 additional day combined with aprepitant; 125 mg orally on the first day of their preparative regimen followed by 80 mg daily on each remaining day of the preparative regimen plus 3 additional days; or dexamethasone 10 mg i.v. once daily and ondansetron 8 mg orally every 8 hours on each day of the preparative regimen plus 1 additional day plus aprepitant placebo. As noted above, the dose of blinded dexamethasone varied because of a known drug interaction between it and aprepitant. Lorazepam was used for breakthrough nausea or vomiting and was allowed as needed for anxiety, catheter insertion, and sleep. Phenytoin [1 g loading dose day 1, then 400 mg daily (days -7 to -2] was used as seizure prophylaxis in patients receiving i.v. Bu/Cy. Prochlorperazine was allowed only for repeated episodes of vomiting (defined as >4 episodes in any 12-hour period).

Assessments

Episodes of vomiting as well as any rescue antiemetics were recorded. Retching was counted as an emetic episode. For the purpose of determining risk factor balance in all arms, patients were asked to fill out a questionnaire pertaining to their history of nausea and vomiting associated with prior chemotherapy, radiation, or pregnancy as well as history of motion sickness or anticipatory nausea and vomiting. Self-grading of nausea was performed daily using a visual analog scale (VAS), a 100-mm line marked no nausea at one end (0 mm) and severe nausea at the other end (100 mm).

Evaluation of Response

The primary efficacy endpoint was to determine and compare the rate of complete response (CR; defined as no emesis with only grade 1-2 nausea: patient able to eat; reasonable intake, using National Cancer Institute Common Toxicity Criteria 3.0) during and 3 days after high-dose therapy in patients treated with aprepitant in addition to oral ondansetron and i.v. dexamethasone compared to the standard regimen of oral ondansetron and i.v. dexamethasone in the stem cell transplant setting. The secondary efficacy endpoints were to compare the degree of nausea, as measured using the VAS, and total number of antiemetic breakthrough doses administered in each arm of the study.

Overall nausea was analyzed by averaging daily VAS scores in each arm of the study. Major and minor responses and failure rates were also determined. Major response (MR) was defined as 1 episode of vomiting or if no vomiting occurred, moderate nausea (intake significantly decreased but patient can eat) with rescue antiemetics allowed. Minor response (mR) was defined as 2 to 4 episodes of vomiting regardless of nausea or rescue antiemetic use. Failure (F) was defined as >4 episodes of vomiting regardless of nausea or rescue antiemetic use. Major efficacy (ME) was defined as complete responders plus major responders. Daily responses were averaged and results are reported as composite scores.

The primary toxicity endpoint was to determine RRT and 1-year survival rate. RRT was measured by documenting engraftment and all non-myelosuppressive grade III or IV toxicity during and after the first 30 days after the completion of the last dose of aprepitant. WBC engraftment was defined as the first day the absolute neutrophil count reached 500/μL sustained for 3 consecutive days, and platelet engraftment was defined as the first of 7 days the platelet count reached 20,000/μL without transfusion.

The definition of CR allowed the use of lorazepam because its use in this patient population was universal for various indications, including anxiety and insomnia; however, an additional analysis was done to determine the percentage of patients with no emesis, less than grade 3 nausea, and no rescue (PRN) medications over the entire 8- to 10-day treatment period.

Statistical Methods

The study design was a stratified 2-sample binomial proportions controlled trial. Based on our earlier hematopoietic stem cell transplant antiemetic study [2], it was estimated that, for the control arm, the absence of emesis during the preparative regimens would be approximately 30%. By modeling based on aprepitant studies in highly emetogenic standard dose chemotherapy, we determined that a complete control rate of 50% would be expected. Based on this, the estimated sample size was 90 patients per arm, which would provide 80% power to detect a difference of 20% between the null hypothesis that both groups have a 30% delayed emesis rate and the alternative hypothesis that the no emesis rate in the experimental group is 50% with a significance level (alpha) of 0.05, using a 2-sided 2-sample *t* test based on the normal approximation to the binomial distribution.

All study variables are summarized using descriptive statistics. Independent *t* tests were used for continuous, normally distributed data to compare the 2 groups. For data that was not normally distributed, the nonparametric Pearson Chi-Square and the Mann-Whitney *U* statistics were used to determine associations between the 2 groups. All nominal data using the 1-year OS and 1-year PFS were calculated using the Kaplan-Meier method, and the difference in survival rate was determined by the log-rank test.

Statistical analyses were performed using SPSS for Windows (SPSS, Inc., Chicago, IL) with significance determined at a 2-sided level of <.05.

RESULTS

Patients

A total of 264 eligible patients were seen during the registration period between September 2004 and July 2008 (Consort Diagram; Table 1). Of these, 181 were randomized into the study. The majority of those not enrolling declined, citing concerns of increased RRT or the potentially diminished efficacy of the transplantation. Two randomized patients never proceeded to transplantation and did not receive the study drug. They are not included in the analysis. Ten patients withdrew consent during the trial (6 in the aprepitant arm and 4 in the placebo arm). Four patients withdrew due to side effects: 1 patient in the placebo arm quit due to a panic attack; 3 patients withdrew in the aprepitant arm due to seizures with visual hallucinations, dizziness, and anxiety, respectively. The remaining 6 patients (3 in each arm) quit due to poor nausea and/or emesis control.

Treatment groups were stratified based on gender and were balanced with respect to age, weight, and history of nausea and vomiting with prior chemotherapy (Table 2). Results of the questionnaire pertaining to history of nausea and vomiting are reported in Supplementary Table S1.

All patients who received the study drug were included in the intent-to-treat analysis. Overall, 1597 of 1644 (97%) VAS

sheets were completed. Lorazepam was our standard breakthrough antiemetic in this trial. Additional breakthrough antiemetics were to be administered only if patients failed lorazepam, which we defined as defined as >4 episodes in any 12-hour period, but were used in 52 of 179 patients (29%), usually because of significant but lesser amounts of nausea after lorazepam, often requested by patient/family members.

Efficacy

For the primary and secondary endpoints, the data was analyzed as composite responses (average daily responses) to account for the different lengths of the preparative regimens, which ranged from 5 to 8 days. Patients who received aprepitant had significantly higher CR rates (81.9% versus 65.8%; $P < .001$) compared to the standard ondansetron plus dexamethasone treatment. Composite MR and ME rates were also significantly higher in the aprepitant arm, while mR and F rates were significantly higher in the control arm (Table 3).

Emesis was controlled to a much greater degree than nausea. Patients receiving aprepitant experienced significantly better complete control of vomiting (73.3% versus 22.5%; $P = .001$) compared to standard therapy. The cumulative percentage of patients with emesis is shown in Figure 1. Fewer total rescue doses were given in the aprepitant arm than in the control arm (594 versus 852; $P = .033$). This is equivalent to an average of 6.6 breakthrough doses per patient in the aprepitant arm versus 9.6 doses per patient in the placebo arm. This difference, however, was not reflected in the subjective measure of nausea; the VAS scores (0-100; with 100 = worst imaginable nausea) were 16.5 mm

Table 1
Consort Diagram

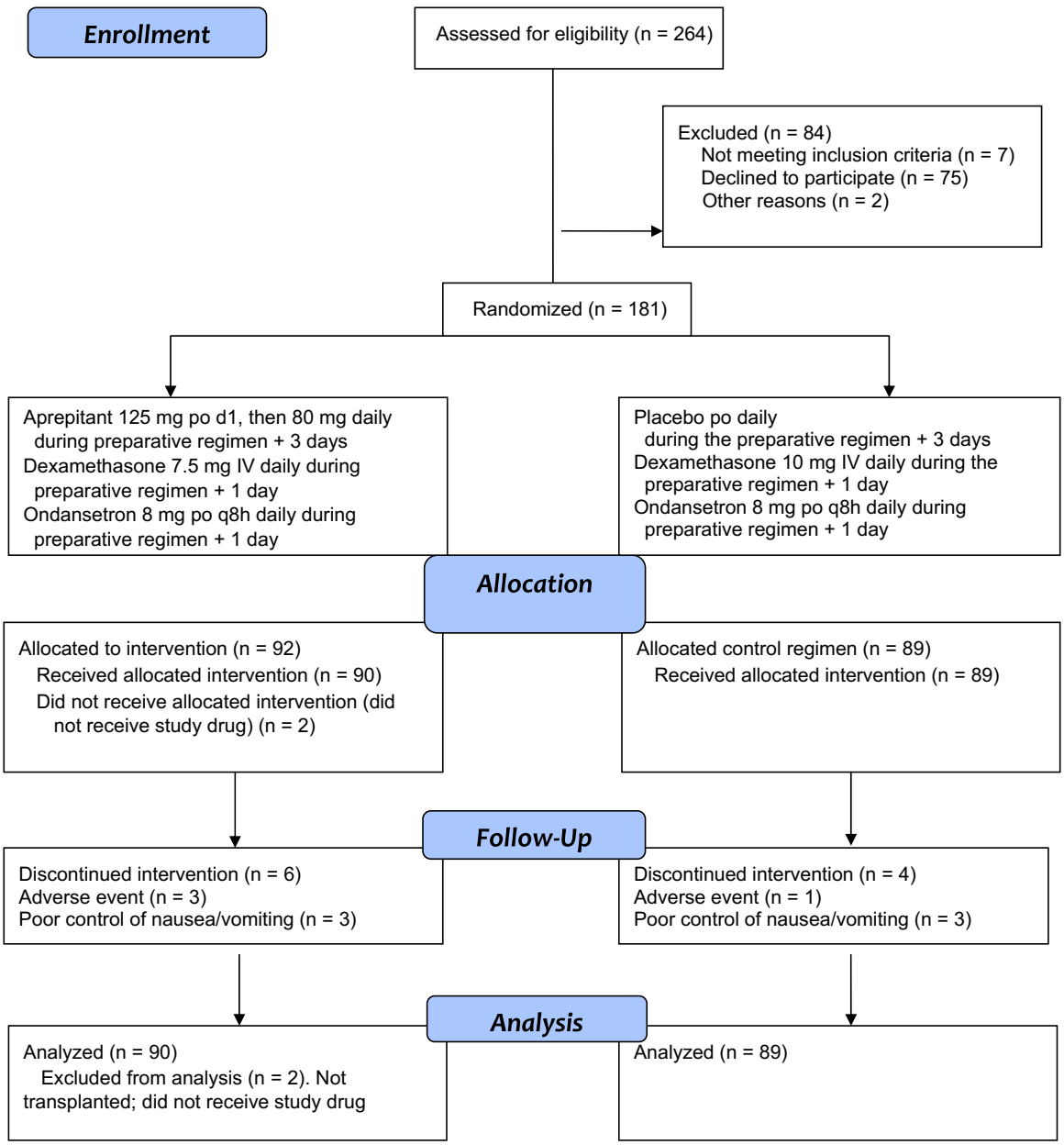

Table 2
Patient Characteristics

	Placebo N = 89	Aprepitant N = 90	*P* Value	Test
Age in years (median)	51 (19-79)	50 (20-75)	.124	*t* test
Weight in kg (median)	82 (59-139)	83 (48-187)	.14	*t* test
Gender				
Male	57	57		
Female	32	33	.921	Chi-square
Diagnosis				
Non-Hodgkin lymphoma	28	29		
AML	22	24		
Multiple myeloma	21	13		
ALL	3	10		
Hodgkin's lymphoma	7	5		
CML	4	2		
Other*	4	7		
Setting				
Inpatient	69	74		
Outpatient	20	16	.433	Chi-square
Graft type				
Auto-PBPCT	48 (53%)	41 (44%)		
Related allo-PBPCT	19	22		
Related allo-BMT	1	1		
MUD PBPCT	8	12		
MUD BMT	6	8		
CORD	7	6	.862	Chi-square
Preparative regimen				
TBI/Cy	33	46		
i.v. Bu/Cy	7	7		
Prescribed orally Bu/Cy	21	13		
TBI/VP/Cy	17	19		
BCV	11	5	.173	Chi-square
History of prior nausea and vomiting with chemotherapy				
Yes	55	59		
No	30	25	.443	Chi-square
History of prior nausea and vomiting with radiation therapy				
Yes	42	41		
No	43	42		
N/A	0	3	.221	Chi-square

AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; Auto-PBPCT, autologous-peripheral blood stem cell transplant; allo, allogeneic; BMT, bone marrow transplant; MUD, matched unrelated donor; CORD, cord as in umbilical cord; TBI, total body irradiation; Cy, cyclophosphamide; Bu, busulfan; VP, etoposide (VP16); BCV, (BCNU, cyclophosphamide, VP16); N/A, not applicable.

* Other diagnoses included myelodysplastic syndrome (MDS), myeloproliferative disorder (MPD), chronic lymphocytic leukemia (CLL), myelofibrosis.

versus 16.9 mm ($P = .892$) in the aprepitant versus control arm, respectively.

As conventional dose chemotherapy antiemetic trials typically report response rates over the entire treatment period, we did these analyses as well. Over the entire treatment period, 48.9% of patients on the aprepitant arm were able to maintain a reasonable intake of food (>50% of normal as recorded by staff nurses) versus only 14.6% of patients in the placebo arm. The vast majority of patients in both arms used lorazepam therapy during the trial (88.9% versus 88.8%; $P = .979$ aprepitant versus control). These percentages represent doses charted as "given for nausea" or presumed nausea when no indication was charted, not doses given before catheter insertion for continuous bladder irrigation or doses charted as given for anxiety or sleep.

Safety

Five patients died in the aprepitant arm due to sepsis (3 patients), toxic epidermal necrolysis and sepsis (1 patient), and veno-occlusive disease of the liver (1 patient), whereas 2 patients died in the control arm due to viral pneumonia/encephalitis (1 patient) and fungal pneumonia (1 patient) within 30 days. All but 1 patient in each group had undergone allogeneic transplants. Noninfectious grade III or IV toxicity (excluding myelosuppression and grade III mucositis) within 30 days of receiving the study drug occurred in 5 patients (Table 4): 3 patients in the aprepitant arm (1 each of a right hemispheric stroke attributed to antilymphocyte globulin, alveolar hemorrhage, and grade IV mucositis requiring intubation) and 2 in the control arm (seizure attributed to busulfan and a presumed pre-existing myelodysplastic syndrome diagnosed day +28). Other nonsignificant differences were heartburn, which was seen in the aprepitant group in 12 of 90 patients versus 6 of 89 patients in the controls, and asthenia in 6 of 90 patients versus 1 of 89 patients (Table 3).

Table 3
Efficacy and Survival

	Placebo N = 89	Aprepitant N = 90	*P* Value
Primary endpoints			
CR % composite (all days)	65.8	81.9	<.001
PFS (months)	28.57	28.33	.727
OS (months)	Not reached	44.4	.5446
Secondary endpoints			
Acute CR % (day 1)	87.6	96.7	.028
No emesis all days %	22.5	73.3	<.001
Average nausea score (VAS) (mm)	16.9	16.5	.892
MR % composite	21.6	16.0	.011
mR % composite	10.3	2.0	<.001
F % composite	2.2	0.1	.001
ME = CR + MR	87.4	97.9	<.001
Time to first emesis-days (mean)	4.5	5.8	.028
Number of PRN doses used	852	594	.033
Additional analyses			
% of patients with no emesis <grade 3 nausea All days-PRNs allowed	14.6	48.9	<.001
% of pts with no emesis <grade 3 nausea All days-No PRNS	11.2	11.1	.979

CR, complete response; PFS, progression-free survival; OS, overall survival; VAS, visual analog scale; MR, major response; mR, minor response; ME, major efficacy; F, failure.
CR = % of days with no emesis, <grade 3 nausea.
Average Nausea Scores (mm) (VAS 0 = no nausea, 100 = worst possible).
MR = % of days with 1 episode of emesis, <grade 4 nausea.
mR = % of days with 2 to 4 episodes of emesis, regardless of nausea.
F = % of days with >4 episodes of emesis.

Aprepitant did not have a negative effect on engraftment. Median time to WBC engraftment was 11 days aprepitant versus 10 days placebo ($P = .778$), whereas time to platelet engraftment was 11 days in both arms ($P = .8206$). Patients in the aprepitant group had a nonsignificant higher (6%) tacrolimus level on the day of transplantation ($P = .5858$), which was not enough to recommend an adjustment of our standard starting dose of 0.03 mg/kg continuous i.v. on day −2.

PFS measured 1 year after transplantation showed no significant difference as shown in Figure 2. Similarly there were no differences in 1 year OS, and the median was not reached. A subset analysis of the 51 patients who received high-dose etoposide as part of their regimen was not powered for significance, but also showed no difference in RRT or outcome.

DISCUSSION

Currently, both the Multinational Association of Supportive Care in Cancer and the American Society of Clinical Oncology recommend only a 5-HT_3 antagonist with

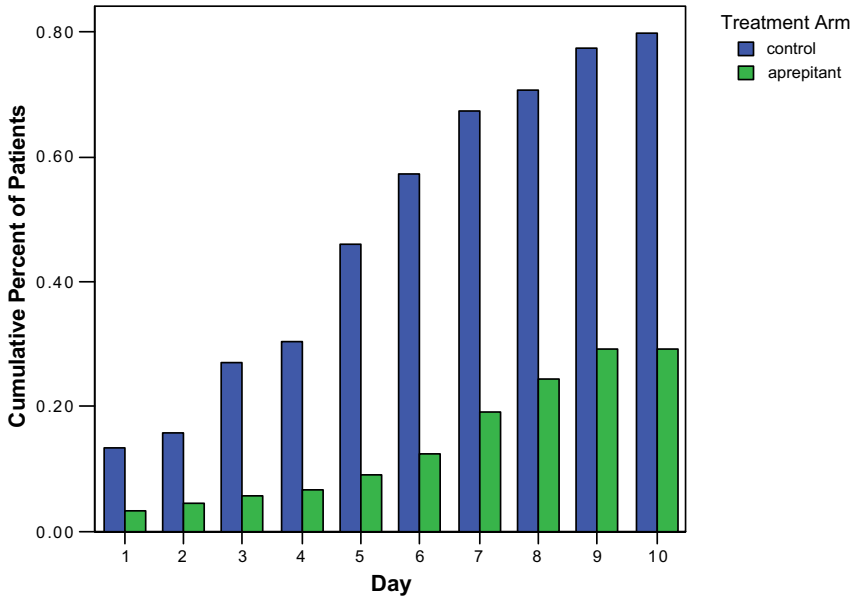

Figure 1. Cumulative percentage of patients with emesis by day.

corticosteroids for patients receiving high-dose chemotherapy [19,20]. This study was conducted to ascertain whether aprepitant decreased the incidence of nausea and vomiting associated with highly emetogenic preparative regimens without negatively affecting patient outcome. We found CR rates (no vomiting, no or mild nausea with breakthrough antiemetics allowed) to be 81.9% of patients receiving aprepitant versus 65.8% placebo ($P < .001$). Complete protection from emesis for the entire 8 to 10 days of treatment was achieved in 73.3% of patients in the aprepitant arm versus only 22.5% of patients in the placebo arm, suggesting that this agent be incorporated into the standard antiemetic regimen for patients who undergo bone marrow transplants.

Similar to standard dose chemotherapy regimens, aprepitant had a much higher impact on emesis than it did on nausea as it neither abrogated the need for rescue medications nor changed the patients' perceptions of nausea as VAS scores were identical between the 2 groups. It did, however, improve the percentage of patients who were able to maintain a reasonable intake of food over the entire treatment period (48.9% versus 14.6% aprepitant versus placebo; $P < .001$).

The ondansetron doses used in this trial were carried over from a previous trial, which found 8 mg of ondansetron every 8 hours as effective as 32 mg i.v. daily. The dexamethasone dose of 10 mg given i.v. daily in the placebo group was dose-reduced 25% (to 7.5 mg) in the aprepitant arm based on the known i.v. methylprednisolone–aprepitant interaction information available when the trial was designed, which showed a similar dexamethasone pharmakinetic profile for patients receiving the identical dose of aprepitant [10].

There are few prospective antiemetic studies using aprepitant in the transplantation setting against which to compare this trial. A small (N = 30) pilot trial by Bubalo et al. [21] reported an overall response rate (CR + MR) of 93% versus 33% for aprepitant versus placebo ($P = .014$) and no emesis in 66.7% versus 33% aprepitant versus placebo ($P = .143$). This study also allowed rescue medications as part of their CR criteria. An open-label noncomparative exploratory trial of 42 patients by Paul et al. [22] found an average 54% complete emetic response rate, which was significantly lower than the 73.3% rate found in our study. Patients in this trial received only 3 days of aprepitant, which is possibly the reason for the lower response rates.

Safety was another important endpoint of this study, given that prolonged administration of aprepitant in the presence of high-dose chemotherapy regimens had the potential of increasing toxic deaths or diminishing the efficacy of the preparative regimens. Cyclophosphamide is an inactive prodrug that is converted to the cytotoxic metabolite 4-hydroxycyclophosphamide by the cytochrome P450 isoenzymes CYP2B6, CYP2C9, and CYP3A4/5 in the liver. This bioactivation is potentially saturable at high doses [23] and could theoretically be negatively affected by aprepitant, which is a moderate inhibitor of CYP3A4 plus a mild inducer of CYP2C9 when used for 3 days, and possibly an inducer of CYP3A4 when used more than 7 days [6]. These changes were not found in aprepitant-treated patients in the clinical

Table 4
Grade III/IV Adverse Reactions

	Placebo N = 89	Aprepitant N = 90
Diarrhea	52	59
Headache	46	44
Fatigue	34	37
Constipation	21	28
Fever	19	22
Hiccups	20	21
Heartburn	6	12
Lightheadedness/dizziness	5	7
Engraftment failure	3 (all PLT only)	5 (3 PLT only)
Weakness	1	6
Pruritus	2	2
Restlessness	0	3
Vasovagal episode	3	0
Hallucinations (1 with seizure*)	0	2
Ileus	0	2
Bloody emesis	2	0
Orthostatic hypotension	1	1
Delayed engraftment	1	0

* Seizure attributed to busulfan.

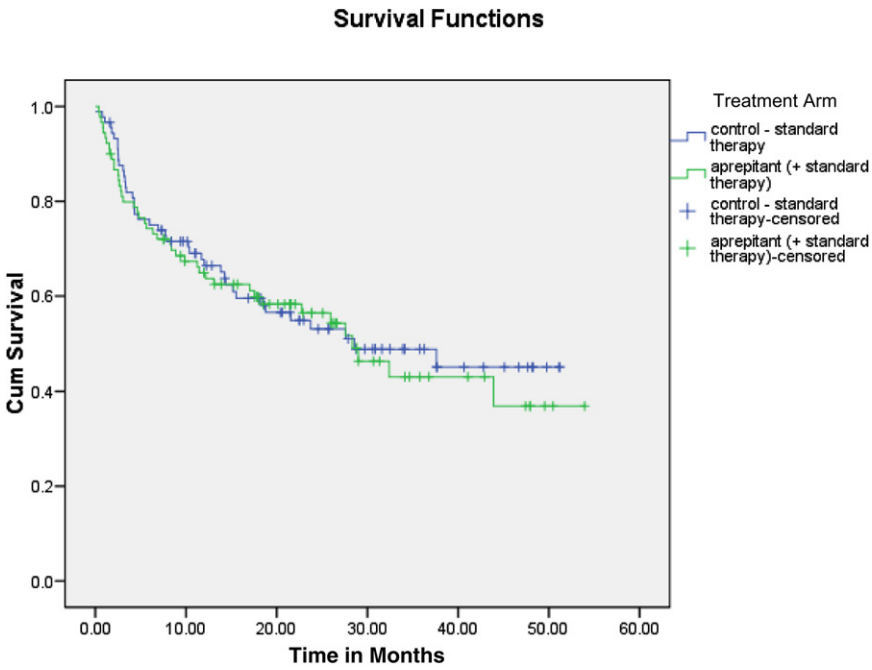

Figure 2. Progression-free survival in all 179 patients ($P = .727$).

study of Bubalo et al. [24] for cyclophosphamide or its metabolites. Considering this and the lack of a difference in 1-year PFS or OS for patients receiving aprepitant versus placebo, we conclude that aprepitant can safely be used with high-dose cyclophosphamide.

We also considered other drug interactions as being potentially significant in this trial. Our study did not have enough patients receiving etoposide to reach a definitive conclusion regarding the safety of aprepitant with high-dose etoposide, which is another agent metabolized by CYP3A4; pharmakinetic studies are recommended. All patients receiving i.v. busulfan also received phenytoin, a strong inducer of CYP3A4 known to decrease aprepitant levels. This interaction seemed to be clinically insignificant as none of the 7 patients receiving this agent experienced any vomiting during phenytoin treatment. Phenytoin was added in this group per the package insert because in dose-finding studies for i.v. busulfan, phenytoin was shown to potentially affect busulfan levels, which at the time of this study were not measured. Of note, only 1 patient on the study died of veno-occlusive disease; however, this patient received the TBI/Cy regimen.

We found that aprepitant was well tolerated; only heartburn and asthenia were more commonly reported in the study versus the control arm. Seven patients (3.9%) died of infection within 30 days of receiving the study medication: 5 in the aprepitant arm and 2 in the placebo arm. It is possible that the prolonged use of dexamethasone up to 9 days as part of the antiemetic regimen used in this study could have, therefore, impacted the infection risks, particularly in the 51.4% of patients undergoing allogeneic transplantation, but this infection risk was no higher than our initial study [2] without aprepitant and we would have expected no imbalance in the 2 arms.

Multiday high-dose preparative regimens are the ultimate challenge of any antiemetic regimen. We found that up to 9 days of aprepitant in combination with ondansetron and dexamethasone significantly decreased the incidence of emesis in this trial, which led to an increase in oral alimentation. However, further research is needed to completely control nausea in this setting. Of note, a recent comparative trial found daily palonosetron to be superior to daily ondansetron in acute myelogenous leukemia in preventing delayed nausea [25]. This suggests that further study of daily aprepitant with palonosetron versus ondansetron in patients receiving multiday high-dose therapy in the transplant may prove even more beneficial than the current novel regimen in eliminating the severe nausea seen in these patients.

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APPENDIX

Supplementary Table S1
Questionnaire Results: History of Nausea and Vomiting

	Placebo* N = 89	Aprepitant* N = 90	*P* Value
Hx of prior nausea and vomiting with chemotherapy			
Yes	55	59	
No	30	25	
Missing response	4	6	.443
Hx of prior nausea and vomiting with chemotherapy			
Mild	30	30	
Moderate	11	17	
Severe	14	11	
N/A	30	25	.614
Missing response	4	7	
Hx of prior nausea and vomiting with RT			
Yes	42	41	
No	43†	42†	
Missing response	4	7	.221
Hx of prior nausea and vomiting with RT			
Infrequent	25	25	
Moderate	8	7	
Severe	12	9	
N/A	40†	44†	
Missing response	4	5	.877
Hx of motion sickness			
No	72	63	
Yes	13	22	
Missing response	4	5	.088
Hx of morning sickness			
N/A	61	61	
No	9	10	
Mild	8	8	
Moderate	3	5	
Severe	4	2	
Very severe/hospitalized	1	0	
Missing response	3	4	.818

Hx indicates history; RT, radiation therapy.

* Entire questionnaire was missing for 3 patients in the placebo arm and 4 patients in the aprepitant arm. Some patients did not answer all questions, likely due to only prior treatment, a tyrosine kinase inhibitor, or no prior treatment. One patient put a question mark near the question of motion sickness.

† The "no" response to question 3 should logically equate to the "N/A" response in question 4, but it did not; patients may have misread the question.